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Equine pituitary pars intermedia dysfunction: current understanding and recommendations from the Australian and New Zealand Equine Endocrine Group

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This statement from the Australian and New Zealand Equine Endocrine Group provides veterinarians with guidelines regarding the pathophysiology, diagnosis and treatment of equine pituitary pars intermedia dysfunction in an Australian context. The foundation of the statement is evidence-based medicine, but if such evidence is conflicting or lacking the panel provides interpretive recommendations based on the panel members collective expertise. The Australian and New Zealand Equine Endocrine Group comprises a community of veterinarians with expertise in the field of equine endocrine disease and the authors are solely responsible for the content.

The purpose of this statement is to provide a review of the current knowledge and opinions about the epidemiology, clinical findings (including sequelae), diagnosis, treatment and monitoring of equine pituitary pars intermedia dysfunction, particularly in the Australian context. This information and the recommendations provided will assist practitioners in making informed decisions regarding the diagnosis and management of this disorder.

Keywords ACTH; horses; insulin; laminitis; pergolide; pituitary pars intermedia dysfunction

Abbreviations ACTH, adrenocorticotrophin; ±-MSH, ±–melanocyte stimulating hormone; BCS, body condition score; CGIT, combined glucose-insulin test; CrNS, cresty

neck score; EMS, equine metabolic syndrome; ID, insulin dysregulation; IR, insulin resistance; NSC, non-structural carbohydrates; OGT, oral glucose test; OR, odds ratio; OST, oral sugar test; PD, pars distalis; PI, pars intermedia; POMC, proopiomelanocortin; PPID, pituitary pars intermedia dysfunction; TRH, thyrotropin-releasing hormone

Pituitary pars intermedia dysfunction (PPID) is the most common endocrinopathy of aged horses.[1,2] There is considerable awareness of this disease among veterinarians and horse owners, in keeping with increased interest in geriatric welfare and health care.[1,3] Although Australian horse population demographic information is limited, one study reported that one-third of horses in Queensland were e 15 years of age,[4], while in an earlier owner questionnaire survey, 18.9% of horses were 16 years of age or older.[5] These findings are similar to equine demographics described for populations in the United Kingdom and North America (reviewed by Ireland, 2016[3]) and, collectively, suggest PPID will be encountered with increasing frequency, given the prevalence of the condition in older animals. In support of this assumption, a greater than 10-fold increase in annual PPID admissions, in comparison with total, was reported to occur over a 12-year period (1993–2004) at University hospitals in North America.[6]

PPID is a neurodegenerative condition that results in loss of dopaminergic inhibition of the pars intermedia (PI) and overproduction of proopiomelanocortin (POMC)-derived peptides, including adrenocorticotrophin (ACTH), ±-melanocyte stimulating hormone (±-MSH), ² -endorphin and corticotrophin-like intermediate peptide, which may be involved in the development of clinical signs of disease.[2] Although PPID is arguably the best known endocrinopathy of horses, aspects of the pathophysiology, epidemiology, diagnosis and

management of the condition remain poorly understood. Recent studies from the Northern Hemisphere have provided important information about seasonal influences on POMC-derived peptides, with implications for the diagnosis of PPID.[7–15] However, extrapolation of this information to the Australasian context is not without risk. Indeed, even within the Northern Hemisphere, a difference in the seasonal responses in ACTH concentration with geographical location was found in one study,[13] while minimal seasonal effect was reported in another study.[15] As such, there is a need for information relevant to the Southern Hemisphere to support best practice for the diagnosis and management of horses with PPID in these geographic regions. Evidence-based approaches to managing PPID will provide opportunities to maximise outcomes and welfare for horses and ponies affected with this disease. The purpose of this statement is to provide information that is relevant to PPID in an Australasian context.

Epidemiology

PPID is a condition of aged horses and ponies. Although the disease may be seen occasionally in animals less than 10 years of age,[10,16] increasing age is a risk factor for PPID,[17] consistent with the neurodegenerative processes involved in the disease[2] and supported by a mean age of PPID animals e 20 years in several studies.[6,7,13,16] The reported prevalence of PPID in aged horses has varied widely between 1.6% and 30%,[13,18–22] and differences may reflect, in part, the diagnostic criteria used, population studied and whether diagnosis was based on owner or veterinary observations. The results of studies in both the UK[20] and Australia[4,17] indicate that under-recognition of PPID by owners occurs, with implications for compromised animal welfare because of delayed veterinary intervention. A

recent study has provided important information that furthers the understanding of the epidemiology of PPID.[17] Using a population of horses aged e 15 years in Australia, the authors found that the prevalence of PPID, based on veterinary examination and plasma concentrations of ACTH and ±-MSH, was 21.2%, and increasing age and owner-reported hypertrichosis were associated with an increased risk of the disease.[17] This prevalence, based on veterinary examination of aged horses in Australia,[17] is similar to reported rates of hypertrichosis in owner surveys performed in Australia,[22] the UK[20,21] and the USA,[18] despite low owner-reported rates of PPID in these studies (1-6-12.6%). Collectively, these findings indicate that despite demonstration of clinical findings indicative of PPID, many horse owners may not recognise these changes as abnormal or sufficiently serious, leading to delays in veterinary examination.[17,20–22]

Although certain breeds, including ponies and Morgan horses, have been considered to be at increased risk of developing PPID,[2] no evidence of breed predilection was found in a recent study.[6] Further, in a study of 325 aged horses in Queensland,[17] neither breed (horse vs pony) nor sex was associated with a diagnosis of PPID, suggesting that apart from age, signalment does not influence the development of PPID in Australian horses. Further, the study by McGowan and colleagues[17] did not contain Morgan horses or details on pony breeds. As such, further epidemiological studies of animal-level risk factors for the development of PPID are warranted to identify animals with an increased predisposition to this disease.

Clinical findings

Commonly described clinical signs of animals with PPID include hypertrichosis, hyperhidrosis, laminitis, polyuria, polydipsia, lethargy and muscle catabolism and weight

redistribution, which can result in loss of epaxial musculature and a potbellied appearance.[2,23,24] An increased susceptibility to secondary infections, endoparasitism and delayed wound healing may occur and seizure activity can be a rare complication of pituitary adenoma.[2] Overall, the clinical findings described for horses with PPID in Australia is similar.[16,17,22] However, further studies are required to determine whether geographical location may influence clinical findings. In a study of 11 cases of PPID in North Queensland, seven horses had anhidrosis, of which four also exhibited heat stress and exercise intolerance.[16] Five of the horses with PPID and anhidrosis were treated with pergolide and exhibited clinical improvement, while the remaining two horses did not receive treatment and clinical signs were unchanged.[16] In addition, 55% of horses with PPID had secondary infections,[16] in comparison with infection rates of approximately 33% in other studies.[2] These findings suggest that the clinical signs of horses with PPID in hot and humid conditions may differ from those in horses residing in regions with temperate climate, with greater risk of thermodysregulation and opportunistic infection, although further studies are required to confirm this.

Laminitis is often the most devastating consequence of PPID, although not all horses with PPID develop clinical evidence of laminitis.[2,16,17,23,24] Although the link between pituitary dysfunction and lamellar pathology is yet to be established, available evidence suggests that PPID-associated laminitis is associated with insulin dysregulation (ID).[25–28] In a study of the lamellar pathology of horses with PPID, all horses with clinical laminitis or a history of laminitis were hyperinsulinaemic, whereas horses without current or previous laminitis did not have lamellar changes when compared with the control groups, suggesting that there may

be subgroups of PPID cases that are at greater risk of laminitis.[27] Laminitis is a common presenting complaint in Australian horses with PPID; in one study, horses e 15 years of age with PPID were more likely to have laminitis (odds ratio [OR] 4.65) and have hyperinsulinaemia (OR 10.4) than aged horses without PPID.[17] These data emphasise that ID can play an important role in PPID, especially with respect to endocrinopathic laminitis, and further information regarding the association between ID and PPID is provided below.

Although the clinical findings of horses with PPID are generally well described, the influences of altered POMC-derived peptides profiles on the development of clinical signs in animals with PPID and inter-relationships between clinical signs and laboratory derangements are unknown.[2] However, as PPID is likely a progressive neurodegenerative syndrome that leads to PI dysfunction, it is possible that a gradual increase in POMC-derived peptide concentrations may be associated with an increased spectrum and severity of clinical signs as the disease progresses. In support of this hypothesis, positive correlations between plasma ±-MSH and ACTH concentrations and the number of historical or clinical findings consistent with PPID were found in a recent study of horses in Queensland.[29]

Diagnosis

PPID

The index of suspicion that a horse has PPID is increased when the clinical signs described earlier are seen. However, only generalised severe acquired hypertrichosis can be used with confidence to definitively diagnose the disease.[30,31] Laboratory testing is used to assist in the diagnosis of PPID, especially when clinical signs are subtle or equivocal. Anecdotally, the dexamethasone suppression test (DST) has been the most common laboratory test used for

the diagnosis of PPID in Australia, with the measurement of endogenous ACTH increasing in favour more recently. The thyrotropin-releasing hormone (TRH) stimulation test is used less frequently for the diagnosis of PPID in Australasia because of difficulties associated with access to TRH, challenges in its preparation and it not being registered for use in Australia. The DST is ideal for testing the function of the pars distalis (PD), the site of biologically active ACTH production. However, it is less well suited to test the function of the PI because biologically hypoactive ACTH, as is thought to be predominantly produced by melanotrophes in PPID, does not respond to exogenous corticosteroids in the same manner as corticotrophs in the PD. As a result, this test has been found to have reduced sensitivity, particularly in cases of early or mild disease ([32,33] Hughes, unpubl. data). When using existing upper limit cut-offs for post dexamethasone suppression of cortisol, seasonality also affects the outcome of the DST and the test has poor specificity during autumn in North America.[33–35] This has also been demonstrated in normal Australian horses (Bailey, unpubl. data). Further, there is some evidence that the specificity of this test is lower than acceptable, irrespective of season.[9,33–35]

The increased production of POMC-derived peptides, as occurs in PPID, is reflected in the systemic circulation. Although there are POMC-derived peptides produced solely by the PI, which would be ideal to measure as diagnostic biomarkers of PPID, ACTH is used because it is extremely well conserved across species and assays to measure this POMC-derived peptide are widely commercially available.[36] The most commonly used immunoassay method for measurement of equine ACTH, the Immulite 1000 (Siemens Healthcare Pty Ltd), is a two-site chemiluminescent immunometric assay that sequentially uses monoclonal and polyclonal

anti-human ACTH antibodies to detect ACTH. In the horse it is likely there are several analogues of ACTH, some biologically active and others less so.[37]

Because horses with PPID are unable to effectively process all of the PI-derived ACTH to smaller peptides, plasma concentrations of endogenous ACTH measured in the systemic circulation are predominantly derived from the PI.[36] In contrast, in clinically normal horses the majority of ACTH measured in the plasma originates from the PD, as ACTH from the PI is cleaved into other POMC-derived peptides and does not reach the systemic circulation.[36] The effect of the circannual cycle on plasma endogenous ACTH in clinically normal horses, when measured by commercially available assays, may be caused by cross-reactivity or interference with other POMC-derived peptides that are produced in greater concentrations during certain times of the circannual cycle, rather than by increased production of ACTH from the PD.[38]

As biologically active ACTH derived from the PD is involved in the production of cortisol, there has been concern that stress or pain at the time of sampling may result in significant variation in ACTH concentrations in normal horses. Two studies have found that plasma endogenous ACTH is not clinically affected by circadian rhythm in horses and for diagnostic purposes sampling can occur at any time of day.[12,39] Stress and pain need to be marked (e.g. strenuous exercise or severe illness) to cause an increase in plasma endogenous ACTH concentration sufficient to decrease the specificity of the test.[40,41] Ingestion of feed has been shown to affect endogenous ACTH and this may be of diagnostic importance when assessing ID using dynamic tests concurrently.[42] However, preliminary research found no significant differences in the basal plasma ACTH concentration if samples were taken at the completion

of an oral sugar test (OST) or a 2-step insulin response test (Bryne, unpubl. data, 2017). Occasionally (≈ 1% of the time), clinically normal horses will have an apparent ACTH concentration well above the reference limit and a specific cause for the elevation cannot be identified.[43] It is not known if this is caused by horse or assay factors.

Variation in ACTH production during a 12-month period was first observed in 2005[9] and further studies have demonstrated that the plasma ACTH concentration in the horse follows a circannual cycle that appears to be broadly related to photoperiod, although other climatic and environmental influences may play a role.[9,43,44] Within this cycle there is a quiescent period where plasma ACTH concentration is lower than during the rest of the year with little variability, and this broadly occurs between the winter and summer solstices. The second phase, the dynamic phase, encompasses the period of the year when the plasma ACTH concentration begins to increase, reaches a peak (acrophase) and then declines (Figure 1).[43] A number of recommendations have been made to determine cut-off values at which a horse would be considered to have an abnormally high plasma ACTH concentration at various times of the year and these values vary according to the study design and locality.[8,,29,43,45] Compared with findings from studies performed in the Northern Hemisphere, the results of two studies[29,43] suggest that clinically normal horses in Australia may have higher endogenous ACTH concentrations at certain times of the year and Australian specific cut-offs are recommended to maximise the specificity of the test (Table 1).

Interpretation of plasma endogenous ACTH concentrations must be performed in view of the clinical presentation of the horse and can be challenging when the values are mildly increased above the upper limit of the reference range and clinical signs are equivocal (i.e. the 'grey

zone'). Interpretation of plasma endogenous ACTH values within the grey zone should be undertaken with caution, especially given that external factors may cause mildly increased concentrations of endogenous ACTH, and repeat testing at a different time of year or more sensitive tests should be used.

In horses with PPID, the plasma endogenous ACTH concentration retains a circannual cycle and the increase in endogenous ACTH concentration seen leading up to and after the autumn equinox is magnified, making this the most reliable time to test because the sensitivity and specificity are higher than at other times of the year.[8,17] The TRH stimulation test is a useful test to consider if increased sensitivity is required for those times of year when ACTH concentrations are lower and less variable, such as during the quiescent phase.[46–48] The cut-off values at which a horse would be considered to have an abnormal TRH stimulation test result as established in the Northern Hemisphere appear to be appropriate for Australia when the test is performed during the quiescent phase of the circannual cycle.[49] This test is difficult to interpret if performed during the dynamic phase of the circannual cycle because ACTH production after TRH administration is often marked and extremely variable between individuals, and testing during that period is currently not advised until further research is undertaken.[49]

Although the use of chemiluminescent assays has allowed clinicians to relax the way equine samples are handled, there are still some considerations that need to be taken into account. Given that plasma ACTH immunoreactivity degrades over time, and degradation is accelerated at higher temperatures, if ACTH is not going to be measured within 4 h of collection the sample should be chilled (ice pack or standard refrigeration) from the point of

collection until processing.[50] Plasma does not necessarily need to be separated, providing the sample does not freeze and will be separated at the laboratory ideally within 8 h and prior to 24 h post collection.[51] If the chilled sample cannot be processed within this time frame, then the sample should be centrifuged and the plasma pipetted into an empty plastic vial (laboratory cryovial or yellow top tube; NB: most red-top tubes now contain a silica clot activator that may affect plasma ACTH concentrations) and transported chilled or frozen. Samples can be frozen at −20°C for 30 days without affecting the plasma ACTH concentration.[51] Although freezing of centrifuged plasma is acceptable, freezing of whole blood or gravity-separated plasma will result in artificially elevated ACTH.[52]

Recommendation. The clinicopathological test of choice for the diagnosis of PPID in Australasia is basal plasma endogenous ACTH concentration and the DST is no longer recommended. Endogenous ACTH is usually measured using a chemiluminescent assay (Immulite 1000, Siemens Healthcare Pty Ltd) and, given the vast travel distances in Australia, it is advised that if a chilled sample is going to take longer than 12 h to reach the laboratory, plasma (ideally centrifuged, although gravity separated is acceptable) rather than whole blood should be sent.

The plasma ACTH concentration has a circannual rhythm and upper reference limits vary throughout the year and may vary geographically (Table 1). To the best of our current knowledge, broadly within Australia, ACTH concentrations determined by the chemiluminescent assay in the context of PPID should be interpreted according to Table 1. As further data become available, broad upper reference limits may become replaced with geographically specific reference intervals. At this time, there has not been sufficient data

collected in New Zealand to determine upper reference limits for diagnosis of PPID. The panel advises that veterinarians in New Zealand consult with their local equine internists with regard to interpretation of test results.

Test results that fall within the grey zone should be interpreted with caution and, depending on the clinical presentation of the patient, retesting during February–April considered. Alternatively, a TRH stimulation test can be performed if the ACTH measurement was undertaken in the quiescent phase (June–November). If treatment is initiated on the basis of the clinical presentation, and the results for the horse is in the grey zone, consideration should be given to withdrawing treatment once the horse is stable for two prior to retesting, as measurement of ACTH concentration while the animal is currently undergoing treatment will not accurately reflect disease status.

Insulin dysregulation

As discussed before, PPID can occur concurrently with ID. In equine medicine, ID is currently defined as hyperinsulinaemia (resting or postprandial) and/or insulin resistance (IR), which may or may not be associated with abnormal plasma glucose dynamics in response to oral or intravenous glucose administration.[53,54] Therefore, ID may be a component of many cases of PPID, as well as being a hallmark of equine metabolic syndrome (EMS).[53] Currently, the EMS phenotype is considered to include regional or generalised obesity, ID and a predisposition to laminitis.[53,55] A horse or pony with ID may exhibit exaggerated insulin secretion in response to oral carbohydrate and/or experience fasting hyperinsulinaemia.[56] However, animals with normal fasting insulin concentrations can also have ID. Tissue IR can occur independently or be accompanied by disruption of the

enteroinsular axis, which manifests as postprandial hyperinsulinaemia in horses/ponies.[58] Following a meal high in non-structural carbohydrates (NSC: sugars, starches and fructo-oligosaccharides), the absorbed glucose simulates insulin secretion from the pancreas. Insulin secretion is also further augmented by the release of incretin hormones from the upper small intestine.[59] This response is markedly increased in animals with ID associated with EMS, resulting in an inappropriately large insulin response to a meal.[58] It is not yet known whether horses with PPID that exhibit ID also produce this increased incretin hormone response.

Although PPID is more frequently recognised in older horses, ID and EMS can occur at any age and are often diagnosed in younger animals.[60] Currently, there is some conjecture about whether EMS may predispose an animal to PPID, or whether the two conditions are unrelated.[2,53] A predisposition to laminitis is common to both EMS and PPID.[61] Regardless, when PPID and EMS occur concurrently in the same animal it has been shown that hyperinsulinaemia may be more marked, which presumably worsens the risk of laminitis.[62] Thus, animals with both conditions require more diligent management and the ability to diagnose whether PPID and ID are both present is paramount. In addition to the tests for the diagnosis of PPID described in this statement, the practitioner should also consider ruling out the existence of concurrent ID. Insulin dysregulation may be associated with either PPID or EMS, and occasionally EMS might occur concurrently with PPID.

Blood tests to assess for ID are also an important part of the clinical assessment of these cases.[63] A basal, fasting blood sample has limited value unless the serum insulin concentration is increased above normal (i.e. > 20 µIU/mL), in which case it may indicate the presence of ID.[63] Subsequent confirmation of IR is not straightforward. Tests that examine

the sensitivity of the insulin-sensitive tissues (muscle, adipose tissue and liver) to insulin action are often difficult and impractical to perform in the field and can be complicated to interpret. In many instances, it may be preferable to refer patients to a specialist facility if this level of work-up is desired/required. However, there are dynamic tests for ID that are reasonably practical for use in the field. To examine the insulin responses to oral NSC a dynamic test that assesses the enteroinsular axis is preferred, because this mimics the response to lush grass or grain diets.[63] The most commonly used test in Australia is an oral glucose test (OGT). This in-field test is simple to perform and can provide valuable information about both the fasting and postprandial insulin concentration in an animal suspected of having ID.[64] The OGT involves feeding 0.75 or 1 g/kg bodyweight of glucose powder mixed with a small amount of bran (≈ 200 g) and lucerne chaff (≈ 0.3% bodyweight).[64] The glucose dose can also be dissolved in water and administered via a nasogastric tube, providing patient stress is minimised. A blood sample is taken before and at 2 h after the meal and placed in plain tubes for analysis of the serum insulin concentration. The postprandial serum insulin concentration is considered to be normal if it is < 80 μIU/mL.[63] Although this test is reasonably repeatable under controlled conditions, it is worth noting that the test is reliant on the meal being fully consumed in a reasonably short timeframe.[64] The palatability of this test meal has been questioned, with some animals reluctant to consume a sugar-laden meal. The use of sucrose (table sugar: a disaccharide composed of glucose and fructose) has not been evaluated for this purpose; however, limited research has indicated that substitution of the glucose with another source of NSC, such as cereals, may be acceptable but further research on more palatable test diets is required.[64,65]

The authors also believe that there is a grey zone around the test cut-off value of 80 μIU/mL and that the practitioner should interpret results close to this value in light of the clinical examination findings. Repetition of the test may be valuable in animals that produce an unexpected result. It should also be emphasised that stress may adversely influence the result, because cortisol and catecholamines may antagonise the effects of insulin.[66]

In the Northern Hemisphere the OST is more commonly used. It is based on the same premise and carbohydrates are administered orally in the form of corn syrup (the most commonly recommended is Karo® light syrup).[67] The typical dose is 0.15 mL/kg of corn syrup, containing a mixture of oligosaccharides from corn starch plus sugars including maltose and glucose. Blood samples during an OST are taken before and 60–75 min after the corn syrup bolus.[67] One advantage of the OST is that the syrup is administered by syringe so theoretically the full dose is administered without relying on voluntary consumption. However, oral dosing can be stressful and suboptimal in some animals. A postprandial serum insulin concentration of 60 μIU/mL has been documented as the cut-off value for making a diagnosis of ID using this test and this lower cut-off value reflects the lower dose of glucose administered.[67] The repeatability of the OST has been reported as reasonable in one study, but not particularly repeatable in another.[68,69] Further, the fasting state of the animal is important to the interpretation of this test, with a lower cut-off value proposed for fed (51 μIU/mL), compared with fasted animals (60 μIU/mL).[69] It has been suggested that the accuracy and repeatability of this test might be improved by giving larger doses of syrup (0.3 or 0.45 mL/kg), although specific cut-off values for the insulin responses have not been

determined.[70] With the current protocol, it may be less likely that a diagnosis of ID is reached when using the OST, compared with the OGT.[71]

A final factor of importance to note when attempting a diagnosis of ID is that the assays available for the analysis of serum insulin concentration in horses are imperfect.[72] This inadequacy stems from the fact that most assays available for insulin analysis are immunoassays that rely on the use of antibodies. Given that no specific equine insulin antibody is currently commercially available, the assays use antibodies directed at another species (e.g. porcine and human). Many studies have demonstrated that the same sample will yield a different insulin concentration when analysed with different assays.[72,73] Thus, it is of the utmost importance for a practitioner to send the blood sample to a laboratory that is experienced in the analysis of insulin in equine samples and that the laboratory has developed its own assay-specific reference ranges. Consistent use of one laboratory is also important to ensure that variability in the result for a single patient is minimised to reduce individual variability when testing is repeated.

Recommendations. In order to determine whether ID or even EMS is occurring concurrently in a patient with PPID, it is important to perform a thorough clinical examination that includes an assessment of adiposity, as well as undertaking dynamic blood testing. The authors therefore recommend the following protocol.

1) Determine the body condition score (BCS)[74] and cresty neck score (CrNS)[75] for the patient:
    - BCS > 7/9 indicates obesity, which may or may not be indicative of EMS

- CrNS > 3/5 indicates regional adiposity and this is a common feature of EMS (although all areas should be examined for fat deposits, including the tail head, shoulder, prepuce/mammary area)
- Many PPID horses or ponies may have low BCS, but may still be ID and prone to laminitis.

2) Perform an in-feed OGT:

- Ensure a basal sample (fasted or following pasture access is OK) is taken prior to the provision of the test meal (as outlined earlier). Collect enough blood to measure ACTH if this has not yet been done.
- Feed 0.75 or 1 g/kg body weight of glucose.
- Take the postprandial sample 2 h after the test meal is fed.
- Place blood in both plain (serum for insulin) and fluoride oxalate (glucose) tubes.
- Send the samples to your preferred laboratory for analysis.

Treatment

Pergolide mesylate is considered the drug of choice for the treatment of PPID and has been used successfully for over 30 years.[23,76] Pergolide is an ergot-derived dopamine receptor agonist (primarily D2, but also D1), which leads to downregulation of the production of POMC-derived peptides.[2] The pharmacodynamic effects of pergolide are rapid, with a statistically significant reduction in plasma ACTH concentration 24 h after commencement of treatment.[77]

Because of individual dosing requirements, it is recommended to start at 0.002 mg/kg per day (1 mg/day for a 500-kg horse) and if there is inadequate improvement in laboratory tests, or

no evidence of clinical improvement after 2 months, then increase the dose to 0.004 mg/kg per day (2 mg/day for a 500-horse). The dose of pergolide should be increased until clinical signs have greatly improved and test results have at least dramatically improved or ideally normalised. Daily dosing is recommended because the half-life ranged from 5.6 to 60 h in a single-dose study[78], and was approximately 24 h in a chronic-dosing study.[79] In the chronic-dosing study,[79] six horses with confirmed PPID were administered pergolide at 0.002 mg/kg PO every 24 h for 2 months, followed by 0.004 mg/kg PO every 24 h for an additional 4 months. Plasma ACTH concentration increased by 50% in three of the six horses 2 days after the last dose and in all six horses by 10 days after the last dose.

An initial side effect of treatment may be inappetence and is reported in 16–33% of cases.[80,81] Most cases of inappetence resolve if the dose is halved for the first 1–2 weeks then gradually increased to the recommended dose.[82] Other less commonly reported adverse effects include signs of depression and diarrhoea. If observed, the drug should be discontinued for 2–3 days and then recommenced at half of the previous dose. The total daily dose can then be titrated back up to the desired dose at 0.5 mg increments every 2–4 weeks. Cardiac side effects that led to the withdrawal of the drug from the human market have not been recognised in horses. There is also evidence that a higher concentration of pergolide may be warranted during the dynamic phase of the ACTH circannual cycle to control clinical signs and normalise ACTH concentrations more rapidly.[79] Mildly affected animals may only require treatment around the acrophase, which may allow for these horses to compete in equine athletic events that perform drug testing at other times of the year.

There is one product, (Prascend™ 1 mg tablets; Boehringer Ingelheim) with a shelf life of 3years registered by both the Australian Pesticides and Veterinary Medicine Authority and the New Zealand Ministry for Primary Industries for the treatment of equine PPID. An additional product (Pergolide 1 mg/5 mL oral suspension; Ranvet, NSW, Aust) with a 6-month shelf life is also registered for use in Australia. Australian Veterinary Association policy guidelines state that compounded products should be only used when there is no alternative registered veterinary product or if the veterinarian considers the use of such compounded medications scientifically justified (and not just based on economic reasons).[83] Pergolide is inherently unstable in the liquid form and research has shown that compounded liquid products should be kept refrigerated in dark containers and used within 30 days of manufacture.[84] Some manufacturers of compounded medications add excipients to improve the stability of their products.

If horses are refractory to treatment and a compounded pergolide formulation is being used, then using a registered formulation is recommended. If laboratory tests and clinical signs have not normalised at a pergolide dosage of 0.006 mg/kg (3 mg/day for a 500-kg horse), then the serotonin antagonist cyproheptadine (0.25 mg/kg PO twice daily or 0.5 mg/kg once daily) may be added or the pergolide dosage can be gradually increased to 0.01 mg/kg (5 mg/day for a 500-kg horse).[60] Cyproheptadine can cause drowsiness, so the lowest dose should be attempted initially.

If medical management is declined by an owner, animals affected with PPID will likely need clipping in the summer months. Special attention to body condition, dentistry and parasite control is essential. Horses with PPID that have a normal insulin status should be fed a senior

diet with pasture grazing and hay supplementation based on body condition. Vegetable oil and cereal grains can also be fed (insulin status should be rechecked periodically if feeding cereal grains or a ration with a high glycaemic index). There is no scientific evidence that any nutraceutical dietary supplement is effective for the treatment of PPID. In addition to medical management, horses with PPID should receive regular care as recommended for aged horses. Regular hoof care is necessary, especially if laminitis has occurred. Laminitis can result in permanent ultrastructural damage to the lamellae. Pergolide will not correct existing hoof wall damage. Horses have had ongoing and first time episodes of laminitis while receiving pergolide therapy, so it is important to warn owners that pergolide therapy may not reduce the risk of laminitis.

If a horse has PPID and/or ID with concurrent obesity, then dietary modification and increased exercise (where possible) should be instigated to induce weight loss. Ideally this will result in a reduced glycaemic response to feeding. The diet of the horse should be carefully evaluated with the aim of restricting the total number of calories in obese horses and reducing the NSC content of dry matter to less than 10%.[55] Pasture access should be eliminated until insulin sensitivity has improved, with a recommended diet consisting of hay fed at 1.5% bodyweight.[55] Ideally the hay should be analysed for NSC content or soaked in cold water for 60 min and the water discarded, which may reduce NSC content.[85,86] Once ID is controlled, limited pasture access may be allowed after evaluation of grass species and growth phase. In general, short (<1 h) turnout periods in the early morning, except after hard frost, will minimise NSC intake.[87] Thin horses with ID may require supplementation with

soaked beet pulp without molasses but with vegetable oils to increase energy density in place of starch-rich ingredients.[55]

The implementation of exercise is dependent on the physical status of the horse, in particular the structure and function of the hoof. In humans, an exercise regimen of approximately 200 min/week of moderate intensity exercise has been demonstrated to increase insulin sensitivity.[88,89] However, data in the equid are conflicting, with some studies suggesting exercise improving insulin sensitivity in the horse[90–93] and others not.[94–96]. A general recommendation is to start with 2–3 exercise sessions of 20–30 min/week, with a subsequent gradual increase in intensity and duration to 5 sessions per week.[55]

Ideally, once PPID is being managed with pergolide, additional pharmaceutical management of ID will not be required. Drugs that may be beneficial if ID is refractory despite appropriate control of all other aspects of PPID include levothyroxine sodium and metformin. Weight loss and improved insulin sensitivity have been demonstrated by administering levothyroxine sodium (48 mg/day PO for horses > 350 kg, 24 mg/day PO for horses < 350kg).[55,97] The dosage should be gradually reduced once ideal body weight has been attained (24 mg/day for 2 weeks and then 12 mg/day for 2 weeks).[55] Metformin (15–30 mg/kg PO 2–3 times daily) has been demonstrated to improve insulinaemic responses through local enteral action rather than systemic effects, as its oral bioavailability is low.[60,98–100]

Recommendations

When clinical signs consistent with PPID are confirmed by diagnostic testing, pharmaceutical management with a registered form of pergolide is recommended. Concurrent ID should also

be managed. If patient welfare (e.g. laminitis) cannot be controlled by medical, dietary and podiatric management then euthanasia must be considered.

Continued monitoring

When monitoring clinical signs the response to treatment is most commonly observed as a decrease in hypertrichosis and laminitis occurrence.[6,101] Other clinical improvements include resolution or reduction of signs associated with anhidrosis, heat stress, foot abscessation, dermatophilosis and infertility; as well as a reduction in lethargy, exercise intolerance, muscle atrophy, hyperhydrosis, polyuria, polydipsia, weight loss and appearance of pendulous abdomen.[6,16,30,101] In one study of horses in the USA, clinical signs did not change in the majority of horses for the first 2 months of treatment.[6] In an Australian study of PPID-affected horses in a tropical climate, resolution of clinical signs took longer (20–30 weeks) when treatment was started in autumn and winter (March–August), than if commenced in spring or summer (September–February).[16]

Baseline diagnostic testing (e.g. plasma ACTH or TRH stimulation test) is recommended, particularly before starting treatment. Plasma ACTH can be rechecked in 30 days to identify spurious elevations or assess the response to treatment. During the dynamic period, clinical signs and ACTH concentration may not substantially improve with standard doses of pergolide until the onset of the quiescent period.[79] In such cases, it may be necessary to more aggressively titrate the dose if more rapid and substantial regulation is desired.[79] Hence monitoring in the dynamic period is highly recommended regardless of the stage of disease and treatment.

It is unclear whether PPID horses treated with pergolide should have ACTH plasma concentrations that return to the normal range or whether a decrease suggests improvement in disease.[30] An association has been found between improvement in hypertrichosis and decreases in plasma ACTH to normal concentrations in horses treated with either pergolide or cyproheptadine.[30] However, another study found no significant difference in ACTH plasma concentrations between untreated horses and those administered pergolide, although clinical improvement was not assessed.[102]

Although PPID may be associated with ID, tests for ID may not be useful to monitor PPID or the response to pergolide treatment.[102] If ID has been concurrently diagnosed, then the appropriate tests (as outlined earlier) should be undertaken with similar frequency to ACTH testing if the horse is stable, disease is well controlled or after any alterations in clinical signs, management or medication or an episode of laminitis.

Recommendation

Monitoring of horses with PPID is recommended twice yearly, with measurement of plasma ACTH concentration during both the quiescent and dynamic period. More frequent evaluation of plasma ACTH concentration is recommended 1 month after commencing treatment, following change in medication or if alterations in clinical presentation are identified. If ID is present, measurement of basal insulin concentration or dynamic testing is recommended concurrently.

Conclusion

This statement provides a review of the current literature and recommendations based on current evidence and opinions of the authors on PPID in an Australasian context.

Conflicts of interest and sources of funding

All authors sit on an advisory board for Boehringer Ingelheim Australia. Cristy Secombe and Rachel Tan have received research funding, travel allowances, speaking honorariums and provided consulting for Boehringer Ingelheim Australia. Allison Stewart has received research funding and has provided consulting and educational material for Boehringer Ingelheim Australia. Melody de Laat has received research funding from for Boehringer Ingelheim International.

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Table 1. Interpretation of upper limits of endogenous ACTH (pg/mL) during the Australian circannual cycle for the geographic localities in southern and northern Queensland

Basal ACTH (pg/mL)	**June–November (quiescent phase)**	**December, January, May (depending on locality may be early or late dynamic phase)**	**February–April (dynamic phase including acrophase)**
Geographic localities south of and including a latitude of 24° south (southern Queensland)			
Negative (not consistent with PPID)	< 40	< 50	< 80
Positive (consistent with PPID)	> 70	> 80	> 120
Grey zone (interpret with caution)	40–70	50–80	80–120
Geographic localities north of and including a latitude of 20° south (northern Queensland)			
Negative (not consistent with PPID)	< 55	< 80	< 100
Positive (consistent with PPID)	> 85	> 110	> 140

Grey zone (interpret with caution)	55–85	80–110	100–140

ACTH, adrenocorticotrophin **/mL**Adrenocorticotrophin.

Figure 1. Circannual ACTH upper reference values and day length change (parametric with robust values for months with non-normal data distribution). Reproduced with permission from Secombe et al. 2017.[43]

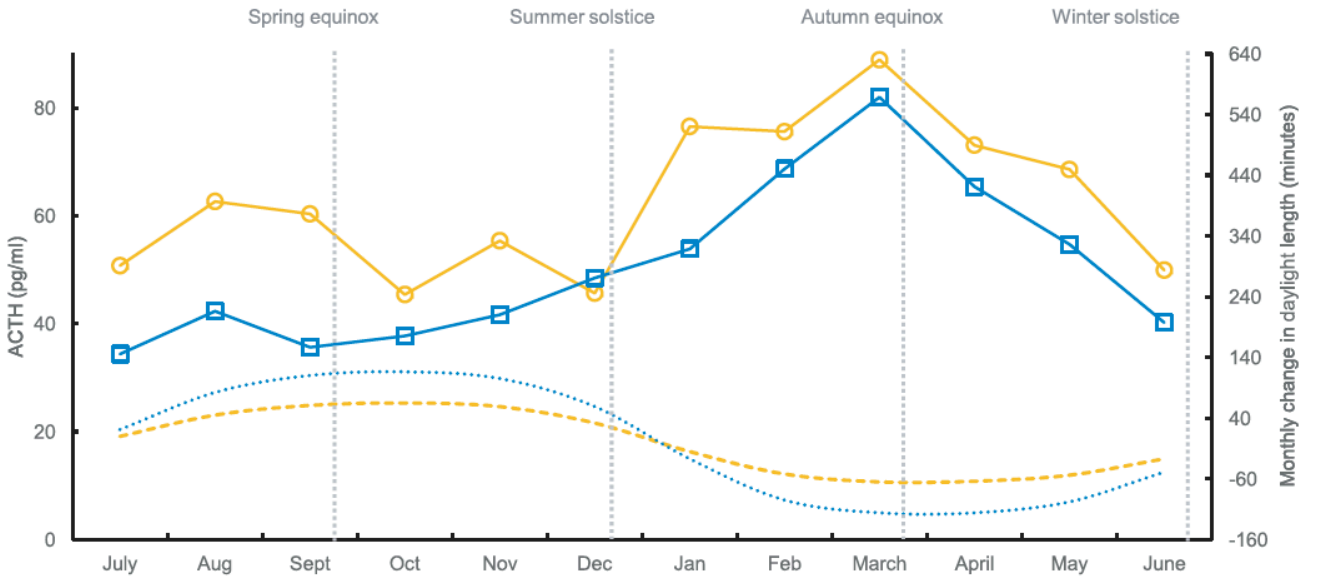

Fig 1. Circannual plasma ACTH upper reference values (Townsville, Perth) and day length change (Townsville, Perth). Parametric with robust values for months with non-normal data distribution.

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